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REVIEW ARTICLES

The Road to Bioabsorbable Stents: Reaching Clinical Reality?

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Abstract

This article provides an overview of the evolution of revascularization devices since Grüntzig's initial introduction of balloon angioplasty in 1977. In-stent restenosis (ISR) is the major shortcoming of conventional (permanent-implant) stent therapy; even with the innovation and promising benefits of drug-eluting stents, management of ISR is very difficult. ISR is mainly caused by the interaction between the blood and the stent surface and a permanent mechanical irritation of the vascular tissue. Thus stenting technology has moved toward the development of temporary implants composed of biocompatible materials which mechanically support the vessel during the period of high risk for recoil and then completely biodegrade in the long term. Preclinical and first clinical experiences with bioabsorbable magnesium stents are discussed.

Key words: Arteriosclerosis—Stents and prostheses—Transluminal angioplasty

From Balloon Angioplasty to Stents: Solving One Problem Creates Another!

Simple balloon angioplasty was first applied in 1977 by Andreas Grüntzig for management of coronary stenosis [1]. This mechanical intervention, named percutaneous transluminal coronary angioplasty (PTCA), was a major breakthrough for the treatment of obstructive coronary artery disease, but was associated with two major pitfalls, namely a high risk of immediate dissection and later risk of restenosis in approximately 50–60% of patients. In 1987 Sigwart described the use of coronary stents [2], which had the potential to treat dissections. The early use of stenting was bridging to open-heart surgeries, but its broader use in treatment of coronary artery disease was impeded by the occurrence of subacute stent thrombosis and complications associated with the aggressive anticoagulant regimen. Colombo subsequently demonstrated that stent thrombosis could be significantly reduced through achievement of high-pressure stent expansion and the combined administration of aspirin and the thienopyridine ticlopidine [3, 4]. Although the technique of optimal stent expansion reduces the incidence of coronary restenosis compared with PTCA, recurrence of luminal narrowing due to in-stent restenosis (ISR) still occurs in approximately 25% of individuals treated, despite major improvements of stent design [5]. The incidence of ISR is particularly high in cases where stents are implanted in complex lesions involving bifurcations, long lesions and small vessels or in patients with diabetes [6, 7]. In addition to the obvious clinical complications imposed by ISR, the lesion sites are effectively inaccessible for subsequent later surgical revascularization. ISR has seriously impeded the success of stent-based interventional revascularization, and defeating ISR has become as important a challenge as defeating restenosis after PTCA.

In-stent Versus Post-PTCA Restenosis

Restenosis, which is defined as ''the arterial healing response after injury incurred during transluminal coronary revascularization,'' is considered a local vascular manifestation of the general biologic response to injury. Iatrogenic injury of the blood vessel leads to the release of numerous vasoactive, thrombogenic, and mitogenic factors which prompt a cascade of molecular and cellular events within the vascular wall, and within this cascade, two major processes can be discerned: arterial remodeling and neointimal hyperplasia [8–11].

Intravascular ultrasound (IVUS) has demonstrated that negative remodeling (shrinkage of the arterial wall diame-

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ter) is the main component responsible for restenosis in post-PTCA lesions [12]. Stents, in providing mechanical scaffolding, have eliminated vessel recoil and restenosis due to long-term negative remodeling following PTCA. However, long-term pressure of the stent struts against the vessel wall is disadvantageous and leads to neointimal tissue proliferation, either focally or diffusely over the length of the stent. IVUS [13, 14] and histology [15, 16] demonstrate that neointimal hyperplasia is the major mechanism of restenosis after stent implantation and the neointima formed is composed principally of proliferating smooth muscle cells and extracellular matrix.

ISR is thus fundamentally different from restenosis associated with PTCA and can be considered as a chronic disease spawned through stenting; tissue repair processes are not only exaggerated due to the high-pressure technique of stent deployment, but also persistently aggravated because the enmeshed wires act as a chronic injury/inflammatory stimulus.

Management of In-stent Restenosis

Ways to manage ISR are either primary prevention (i.e., avoid the use of stents) or the development of concomitant or adjunctive interventional therapies. However, treatment of ISR is extremely difficult. Techniques available to treat ISR include balloon angioplasty, cutting balloon angioplasty, rotational coronary atherectomy, directional coronary atherectomy, excimer laser catheter ablation, repeat bare stent implantation, brachytherapy, and, more recently, drug-eluting stents (DES) [9–11, 17]. These various techniques may be used either individually or in combination. For the most part, mechanical and radiation-based therapies have been used to treat ISR, whereas drug and stent-based therapies have been used in de novo lesions to try to prevent ISR. The most promising therapies are brachytherapy and DES, which target the principal cause of ISR, namely neointimal proliferation.

Brachytherapy has established itself as a viable modality to treat ISR [18–20], resulting in an appreciable decline in restenosis rates to approximately 10–15% [10, 21]. However, it is associated with significant deleterious effects including a risk of late thrombosis [22, 23] and edge restenosis [24].

Heparin-coated stents, with the purpose of limiting stent thrombosis, represented the first generation of DES [25]. Numerous pharmacologic compounds with either anti-inflammatory, antiproliferative or antimigratory properties have since been tested for their potential to inhibit restenosis [11, 26–29]. The compounds include sirolimus, tacrolimus, everolimus, micophenolic acid, ABT-578, biolimus, paclitaxel, tyxane, QP2, dexamethasone, 17-beta-estradiol, batimastat, actinomycin D, methotrexate, angiopeptin, tyrosine kinase inhibitors, vincristine, mitomycin, and cyclosporin. Most of the substances have yielded disappointing results, with the exception of antineoplastic agents. The most promising of these are the natural macrocyclic lactone sirolimus (rapamycin) and analogs (tacrolimus, everolimus, micophenolic acid), which induce cell cycle arrest in the late G1 phase and thereby inhibit cell cycle progression, and the lipophilic diterpenoid taxol (paclitaxel, taxane), which enhances microtubule assembly, resulting in inhibition of cellular replication. Use of these compounds in DES has seen a marked reduction in the incidence of ISR after coronary stenting to between 4% and 15% [11, 21, 27–29]. On the other hand, the SCIRROCO I trial on use of sirolimus-coated DES in peripheral arteries did not reveal major benefits in the long term [30]. Differences in vessel size and lesion area may contribute to the discrepant success of DES between coronary and peripheral vessels [31]. SCIRROCO I did indicate better results in a subgroup given a slow-release form of sirolimus and a further trial (SCIRROCO II) is under way.

Although results from large randomized studies with long-term follow-up (>5–10 years) after use of DES are not yet available, it has become obvious that permanent stents per se generate problems other than just IRS. DES can indeed overcome much of the ISR due to neointimal hyperplasia, but permanent metallic implants have specific drawbacks which limit their more widespread use. These limitations include long-term endothelial dysfunction, delayed re-endothelialization, thrombogenicity, permanent physical irritation, chronic inflammatory local reactions, mismatches in mechanical behavior (vasomotion) between stented and nonstented vessel areas, inability to adapt to growth, and importantly nonpermissive or disadvantageous characteristics for later surgical revascularization [8, 27, 29]. These biological limitations arise through stent–host (blood and tissue) interactions, the mechanisms of which remain poorly understood. However, an important factor restricting biocompatibility concerns technical aspects of the device. Stent design and material composition, physicochemical characteristics of the stent, including surface energy, electrical surface charge, surface texture, and surface chemistry, significantly affect stent–host interaction phenomena [32, 33].

The Concept of Bioabsorbable Stents

Stents composed of bioabsorbable/biodegradable material represent an alternative revascularization modality, the justification being the short-term need for a vessel scaffolding and avoidance of the potential long-term complications of metal stents [34, 35]. Although the idea of biodegradable stents is not new and has been actively pursued experimentally since metal stents were first introduced, the emergence of a viable degradable stent has been relatively sluggish. This is largely due to difficulties in developing an adequate biodegradable material that is compatible with the vessel wall and does not evoke a significant

inflammatory response, leading to worse restenosis than is caused by a metal stent. Some theoretical limitations of this technique have to be considered. It is not known how long a stent needs to remain mechanically stable after placement in a diseased artery. Another issue is the rate and the mechanism of degradation of a stent placed in front of a major collateral, such as for kissing aortoiliac stents, or across the common external iliac arteries. Furthermore, the short- and long-term local intramural biocompatibility and bioreactivity of the constituents of biodegradable materials during degradation need to be assessed.

Ideally degradable implants should offer better physiologic repair, reconstitution of local vascular compliance, a temporary, limited longitudinal and radial straightening effect, and the possibility for growth and late positive remodeling [17, 35–37]. They should be compatible with follow-up MRI and IVUS procedures and not restrict surgical revascularization. Biodegradable implants should also offer the possibility for integration with local drug delivery and genetic transfer.

Bioabsorbable Polymer Stents

The prototype of a temporary stent was a bioabsorbable, self-expanding poly-*l*-lactic acid stent as introduced by Stacks and colleagues of Duke University for the reduction of post-PTCA experimental restenosis [38–40]. Although minimal inflammation using the poly-*l*-lactic acid stent in a dog model was demonstrated [34], other biodegradable polymers including polyglycolic acid/polylactic acid, polycaprolactone, polyhydroxybutyrate valerate, polyorthoester, and polyethyleneoxide/polybutylene terephthalate were subsequently tested in a porcine model and found to induce significant inflammatory and arterial proliferation after implantation [41]. These adverse tissue responses may be attributable to a combination of parent polymer compound, biodegradation products, and possibly implant geometry.

A subsequent stent (Igaki-Tamai stent) composed of high molecular weight (321 kDa) poly-*l*-lactic acid and with a novel zigzag helical coiled design (as opposed to a mesh design) produced acceptably low inflammatory and scarring responses after experimental [42] and clinical implantation [43]. Some concerns have been raised related to slow absorbability of the stent, possible thrombosis arising from damage to the vessel wall through the heat produced by the initial stent expansion, and possible hyperplasia arising through vessel wall trauma from the chronic swelling produced by continued stent expansion [17, 35].

Drug-loaded polymer stents have also been tested in porcine coronary arteries. Both a tyrosine kinase antagonist (ST638)-coated Igaki-Tamai stent [44] and a double helical poly-*dl*-lactic acid stent containing the antiproliferative substance paclitaxel [45] were shown to reduce the degree of stent-induced restenosis, although the problems of inflammation remained.

A variety of polymer-based absorbable stents are currently being commercially developed. These include a balloon-expandable and self-expanding poly-*l*-lactic acid stent (Guidant), an everolimus-coated self-expanding poly-*dl*-lactide stent (Biosensors), and a tyrosine-derived carbonate stent with a radiopaque iodine backbone (Reva Medical). Nevertheless, important drawbacks of polymer stents relate to their intrinsic mechanical properties. Polymers are not able to guarantee the same radial force and limited recoil compared with metal platforms, and their relative bulkiness could limit application in small vessels.

The Bioabsorbable Iron Stent

Peuster et al. [46] were the first to examine the feasibility and safety of degradable metallic stents in endovascular stenting. They developed a corrodible iron stent (NOR-1) that was produced from pure iron (> 99.8% iron) and laser-cut into a slotted tube design similar to a commercially available permanent stent (PUVA-AS16). The stents were implanted into the native descending aorta of 16 New Zealand white rabbits. Peuster et al. reported a maintained stent patency, no thromboembolic complications, and no adverse events during a 6–18 month follow-up period. Histopathologically there was no significant evidence of either an inflammatory response or neointimal proliferation, and organ examination did not reveal any systemic toxicity. Although this initial in vivo experience would suggest that degradable iron stents can be safely used, further studies are clearly necessary.

The Bioabsorbable Magnesium Alloy Stent

Heublein and colleagues conducted pioneering investigations on the suitability of the magnesium alloy AE21 as a biodegradable metallic-stent platform [37]. The magnesium alloy was expected to satisfy most mechanical, biocompatibility, and degradation/absorption performance requirements of a degradable vascular implant. AE21 is composed of a specific magnesium alloy containing 2% aluminum and 1% rare earth metals (Ce, Pr, Nd). Magnesium was chosen as the main alloy component because of its hypothrombogenic properties and predictable local tissue tolerance [47]. Additionally, the mechanical properties and corrosion of magnesium alloys are reasonably controllable under physiologic conditions [48]. Adverse side effects of alloy degradation products were expected to be minimal. Magnesium is the fourth most plentiful cation in the body and its role in biological systems has been investigated extensively [49]. In both the Hubelein prototype and the modified stent developed by Biotronik (see below) the amount of magnesium per stent is 3–6 mg (depending on length). Slow stent degradation should not harm tissue, since, assuming degradation over several months, the concentrations of released

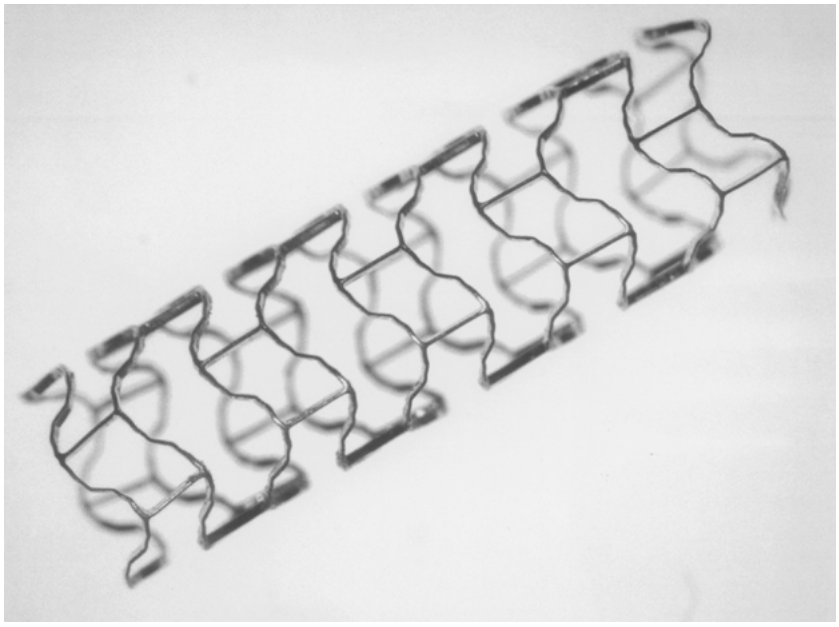

Fig. 1. Absorbable Metal Stent (Magic 3.0/10, Biotronik) fully dilated.

magnesium would be negligible in comparison with the physiologic plasma magnesium content of 1.4–2.1 mEq/l (0.70–1.05 mmol/l). Magnesium can also undergo a normal metabolic conversion to chloride, oxide, sulfate or phosphate salts, which when given parenterally at doses of up to 0.5 mol/l are well tolerated. Moreover, a magnesium deficit significantly contributes to cardiovascular disease, and its slow release during stent degradation can be expected rather to have beneficial effects. There is ample evidence [50–56] that magnesium acts as a systemic and coronary vasodilator and is integrated in many metabolic processes such as muscle contraction; it is a cofactor of ATPase and acts as a physiologic calcium antagonist, thereby preventing intracellular calcium overload in ischemia and platelet aggregation [57, 58]; magnesium reduces the vascular resistance, which subsequently increases the cardiac index; and a high extracellular magnesium concentration not only reduces the vascular tone in the systemic, coronary, and pulmonary vasculature but also lowers the systemic blood pressure.

Implantation of the magnesium alloy stent prototype in a porcine model demonstrated very low thrombogenic and inflammatory responses and predictable degradation kinetics [37]. Significant neointimal proliferation was evident, but this disadvantage was offset by later positive remodeling. Since the alloy did not influence endothelial cell proliferation in vitro [37], there should also be competent re-endothelialization in vivo.

Biotronik subsequently developed a modified magnesium-alloy-based Absorbable Metal Stent (AMS) consisting of magnesium (>90%), zirconium, yttrium, and rare earth elements. The stent (Magic, Biotronik) is pre-mounted on a fast-exchange delivery system, compatible with 6 Fr introducer systems. The tubular, slotted, balloon-expandable stent is sculpted by laser from a single tube of a bioabsorbable magnesium alloy. The stent design (Fig. 1) was specifically developed with respect to the mechanical characteristics of the magnesium alloy in order to achieve a radial force comparable to conventional metal stents. The AMS is rapidly proving itself to be remarkably successful. In a first pilot study, 12 absorbable (AMS) and 6 conventional metal stents (control) were implanted in the main coronary arteries of mini-pigs without any complications. Quantitative coronary angiography revealed significant higher minimal lumen diameter values for the AMS (1.50 mm) than the control stents (1.26 mm) at 4 weeks follow-up and values of 1.55 mm versus 1.09 mm at 8 weeks follow-up, respectively. Histomorphometric analysis at 8 weeks showed significantly reduced intimal proliferation for the AMS in comparison with the control stent, indicating a reduced mechanical irritation of surrounding tissue as well as possible antiproliferative effects of the stent material. No stent-related adverse events occurred during the study. No thrombotic effects and acceptable local inflammation response were observed. In a short-term trial, endothelialization of the AMS struts was almost complete after a few days. Mechanical integrity of the AMS did not change appreciably within this time frame under in vivo conditions. In order to evaluate the biological reaction, patency, and efficacy of the AMS over 12 months, a study in 33 mini-pigs was performed in 2004.

With proven device safety and a proper basic performance of the absorbable metal stent in preclinical trials, the first clinical application of the device was initiated. Twenty patients with critical limb ischemia of Rutherford class 4 and 5 and lesions in below-the-knee section of infrapopliteal arteries were treated with absorbable metal stents by Peeters et al. [59]. This angioplastic intervention was an attempt to prevent amputation of the limb by restoring sufficient blood flow to the lower leg. Absorbable metal stents (3.0 mm/15 mm) were implanted under angiographic control. The

proper positioning and homogeneous inflation of the stents was controlled by IVUS at the end of the procedure. Blood parameter analyses were performed postprocedurally. The blood flow through the stented area was assessed using color flow Doppler ultrasound (CFDU) measurements at discharge, and at 1 and 3 months after the procedure. In addition, MRI recordings have been performed at discharge, and at 1 and 3 months after the procedure. Blood parameter analysis did not provide any evidence for possible toxic reactions to the stent material. Preliminary data after 3 months yielded a primary clinical patency of 89.5%. No major amputation was necessary, yielding a limb salvage rate of 100%. Serial imaging with CFDU as well as MRI showed a decreasing intensity of the stent structure. A comparison of the postprocedural and follow-up images clearly indicated the ongoing absorption process of the AMS. In summary, the first clinical experience with absorbable metal stents was completely safe, indicating a promising performance of this new stent system [59].

Given the positive experience in limb ischemia, the first coronary clinical study has been initiated. This study, PROGRESS-AMS, intends to collect first data on the feasibility of absorbable metal stents in the treatment of coronary artery lesions in man. It is planned to enroll 63 patients in various centers worldwide. The primary endpoint is MACE (Major Adverse Cardiac Events) after 4 months. Secondary endpoints include procedural success, angiographic outcome at 4 months, and clinical performance after 4 and 12 months post-procedure. The patient enrollment phase in this trial is ongoing. Procedural success in the first patients was good and procedures were free of complications. The handling of the absorbable metal stents was not different from that of conventional stents. The lack of X-ray visibility of the stent did not negatively affect the implant procedure. Angiographic results will show to what extent the AMS succeeds in combining a good performance in terms of restenosis prevention with the advantage of degradation and the related implications.

Conclusion

Experimental and early clinical testing has encouragingly shown that bioabsorbable coronary stents offer a real possibility to dramatically improve both the acute and long-term results of percutaneous coronary revascularization. Although the long-term beneficial outcome in controlled clinical studies has yet to be demonstrated, it can be anticipated that magnesium-alloy-based biodegradable stents offer the possibility for integration with local drug delivery, genetic transfer, and radiation. Furthermore, an eventually proven successful use of drug/gene-loaded biodegradable stents in revascularization has enormous translational impact for use of geometrically modified biodegradable implants as potential therapeutic carriers for treatment of diseases (e.g., cancers) where specific tissue targeting and high local dosage possibilities could offer an alternative to conventional systemic therapies.

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